RESPONSE

I. Status of the Claims

Claim 5 has been amended. Claims 1-5 are therefore presently pending in the case. For the convenience of the Examiner, a clean copy of the pending claims is attached hereto as Exhibit A and a marked-up copy of the pending claims is attached hereto as Exhibit B.

II. Support for the Amended and New Claims

Claim 5 has been amended to more clearly claim aspects of the invention. Amended Claim 5 finds support throughout the specification as originally filed, with particular support being found at least at page 13, lines 2-8.

As the amendment of 5 is fully supported by the specification and claims as originally filed, it does not constitute new matter. Entry therefore is respectfully requested.

III. Rejection of Claims Under 35 U.S.C. § 101

Claims 1-5 are rejected under 35 U.S.C. § 101 because the claimed invention lacks specific and substantial utility for the reasons set forth in the prior Office Actions, Paper No. 8 and 10. Applicants persist in their traverse for the reasons described in previous responses and those reasons described below.

The Action disagrees with Applicants' logical assertion, based on the evidence, that the sequences of the present invention encode a novel human metalloprotease, specifically metallopeptidase M3, neurolysin. Applicant clearly asserts this identity in the original specification. First in the title of the original application NOVEL HUMAN METALLOPROTEASE AND POLYNUCLEOTIDES ENCODING THE SAME. Second, in the background information section of the specification, Section 2, Applicants describe the activity of metalloproteases including neurolysin. Thirdly, as emphasized in the instant Action (page 2), the Applicant identifies the structural similarities between mammalian neurolysin proteins and the sequences of the present invention.

In previous responses, Applicants have provided several pieces of evidence that those of skill in the art would find Applicants assertions credible. That evidence clearly shows that those of skill in

the art, in no way affiliated with Applicants, when faced with the same information, would and did identify the sequences of the present invention as a metalloprotease, neurolysin. Thus those of skill in the art agree with Applicants' assertion and would, therefore, clearly find Applicants' assertion credible. The fact that these supporting identifications were not published until after Applicants' effective filing date supports Applicants' priority position. However, it does not discredit the position that these identifications corroborate Applicants' identification of the sequences of the present invention as a metalloprotease, more specifically a neurolysin.

The many identifications by those of skill in the art clearly indicates that Applicants' assertions are credible. Given the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable, this is clear evidence that those skilled in the art would have recognized the function and activity of the protein encoded by the sequences of the present invention, there can, therefore, be no question that Applicants' asserted utility for the described sequences is "credible." According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

Included in the Action's reasons for the alleged lack of utility of the present invention is the statement that "However, Applicants themselves did not present any evidence that protein of SEQ ID NO:2 is able to cleavage neurotensin between residues Pro10 and Tyr11, and to bind angiotensin; the assays are easy to perform *in vitro*." However, the ease of potential experimentation is not the issue, this emphasis is misplaced as it has long been established that "there is no statutory requirement for the disclosure of a specific example". *In re Gay*, 135 USPQ 311 (C.C.P.A. 1962). Applicants assertion of the stated utility is legally sufficient and should control the utility analysis unless the Examiner meets the burden of establishing the lack of utility by making evidence of record that conclusively refutes the Applicants asserted utility.

Additionally, the real world utility of the present invention is demonstrated by results obtained when a knockout mouse was made in which the mouse gene encoding the ortholog of SEQ ID NOS: 1 and 2 of the present invention (human neurolysin (metallopeptidase M3 family) was disrupted by homologous recombination. These knockout mice were subject to a medical work-up using an

Is it theirs?

integrated suite of medical diagnostic procedures designed to assess the function of the major organ systems in a mammalian subject. Disruption of the mouse gene of the present invention and thus elimination of the protein it encodes, resulted in reduced viability of the homozygous (-/-) deficient mice. The surviving homozygous (-/-) deficient mice exhibited an increased anxiety-like response, as manifested as a decreased sum center-to-total distance ratio and decreased center-to-total distance travel during all intervals tested when compared with their wild-type (+/+) littermates. Homozygous (-/-) mice deficient in the gene and protein of the present invention also demonstrated decreased paw flinching during phase II of a formalin pain assay, as compared to their wild-type (+/+) littermates, suggesting decreased sensitivity to tonic or chronic pain. This clearly provides evidence that the nucleic acid and protein of the present invention have a biological function and the molecules of the present invention as well as agonists or antagonists directed at them can be used to diagnose and treat anxiety and pain disorders and are clear, validated drug targets. Thus clearly the molecules of the present invention also has real world substantial and specific utility.

The Action also discounts Applicants' assertion regarding the use of the presently claimed polynucleotides on DNA chips, based on the position that such a use would allegedly be generic. Further, the Action seems to be requiring Applicants to identify the biological role of the nucleic acid or function of the protein encoded by the presently claimed polynucleotides before the present sequences can be used in gene chip applications that meet the requirements of § 101. Applicants respectfully point out that knowledge of the exact function or role of the presently claimed sequence is not required to track expression patterns using a DNA chip. As set forth in Applicants First Response, given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. The claimed sequence provides a specific marker of the human genome (see evidence below), and that such specific markers are targets for discovering drugs that are associated with human disease. Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as the specification details. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, as well as more recently issued U.S. Patent Nos. 5,837,832, 6,156,501 and 6,261,776. Accordingly, the present sequence has a specific utility in such DNA chip

applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequence, must also be useful.

Additionally, since only a small percentage of the genome (2-4%) actually encodes exons, which in-turn encode amino acid sequences. Thus, not all human genomic DNA sequences are useful in such gene chip applications, further discounting the Examiner's position that such uses are "generic". Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101. It has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971).

Evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company, Rosetta Inpharmatics, was viewed to have such "real world" value that it was acquired by large pharmaceutical company, Merck & Co., for substantial sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

The sequences of the present invention have particularly specific utility in DNA gene chip based analysis as they have been identified to contain several coding region single nucleotide polymorphisms

(cSNPs), thus increasing their utility in DNA gene chip based analysis. The first identified polymorphism, the "y" at position 951 of SEQ ID NO:1 represents a translationally silent C or T polymorphism. A second identified polymorphism, the "y" displayed at position 2,110 of SEQ ID NO:1 represents a C or T polymorphism that can result in either a P or a S at corresponding amino acid position 704 of SEQ ID NO:2.

Further evidence of utility of the presently claimed polynucleotide, although only one is needed to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), is the utility the present nucleotide sequence has a specific utility in determining the genomic structure of the corresponding human chromosome, for example mapping the protein encoding regions, as described in the specification and evidenced below. Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of the human chromosome containing the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences (see evidence below). In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence.

Only a minor percentage of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Applicants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence in support of the Applicants' position, the Board is requested to review, for example, section 3 of Venter *et al.*

(*supra at* pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article.

As still further evidence supporting Applicants assertions of the specific utility of the sequences of the present invention in localizing the specific region of the human chromosome and identification of functionally active intron/exon splice junctions is the information provided in **Exhibit C**. This is the result of a blast analysis using SEQ ID NO:1 of the present invention when compared to the identified human genomic sequence. This result indicates that the sequence of the present invention is encoded by 13 exons spread non-contiguously along a region of human chromosome 5, which are contained within partially overlapping clones, AC016643.6 and AC008958.7. Thus clearly one would not simply be able to identify the 13 protein encoding exons that make up the sequence of the present intention from within the large genomic sequence. Nor, would one be able to map the protein encoding regions identified specifically by the sequences of the present invention without knowing exactly what those specific sequences were.

In addition to the previously submitted Exhibits, demonstrating that the sequences of the present invention encode a metalloprotease, neurolysin. Genetic mapping of the sequences of the present invention maps to human chromosome 5, at the very same region as that to which neurolysin (NLN) has been mapped.

Therefore, in addition to the clear sequence homology between molecules annotated as neurolysin, a metalloprotease, and the sequences of the present invention which have been evidenced. The sequences of the present invention and neurolysin (NLN), map to the same genetic locus, 5q12.2.

Finally, the requirements set forth in the Action for compliance with 35 U.S.C. § 101 do not comply with the requirements set forth by the Patent and Trademark Office ("the PTO") itself for compliance with 35 U.S.C. § 101. The PTO has issued numerous patents on polynucleotide sequences that have not been directly shown to be associated with the function of the protein that is set forth in the specification, the condition apparently set forth by the Examiner as allegedly necessary to comply with 35 U.S.C. § 101. The Examiner is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,2812 (each of which claims short polynucleotide fragments), and recently issued U.S. Patent No. 6,340,583 (which includes no working examples). None of these issued U.S. Patents contain examples

of the "real-world" utilities that the Examiner seems to be requiring in the present Action. Applicants understanding is that issued United States patents retain a legal presumption of validity which in this case indicates that the inventions claimed in the cited patents are *legally presumed* to be in full compliance with the provisions of 35 U.S.C. sections 101, 102, 103, and 112. Applicants respectfully submit that, absent a change in the law as enacted by Congress and signed by the President, it is improper for the Examiner to hold Applicants' invention to a different legal standard of patentability. Given the rapid pace of development in the biotechnology arts, it is difficult for the Applicants to understand how an invention fully disclosed and free of prior art at the time the present application was filed, could somehow retain *less* utility and be *less* enabled than inventions in the cited issued U.S. patents (which were filed during a time when the level of skill in the art was clearly lower). Simply put, Applicants invention is *more* enabled and retains *at least as much* utility as the inventions described in the claims of the U.S. patents of record. Any argument to the contrary is at best arbitrary and at worst capricious. Absent authority provided by an act of Congress or Executive order, arbitrary or capricious conduct by an administrative office of the U.S. government has historically proven to conflict with the provisions of the U.S. Constitution. The Patent Office does not have the authority to rewrite U.S. law. However, the Patent Office does have a Constitutional obligation to administer U.S. law in an unbiased and procedurally consistent manner. As the issued U.S. Patents cited above are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph, Applicants respectfully submit that the presently claimed polynucleotide must also meet the requirements of 35 U.S.C. § 101.

For each of the foregoing reasons, Applicants submit that in light of the above discussion and those presented in previous Applicant responses, the presently claimed invention has been shown to have a substantial, specific, credible and well-established utility and that the rejection of pending claims 1-5 under 35 U.S.C. § 101 has been avoided, and respectfully request that the rejection be withdrawn.

IV. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 1-5 are also rejected under 35 U.S.C. § 112 first paragraph. Since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

The Examiner states (Action at last line of page 3) "That are Chen et al. who demonstrated that human protein having the amino acid sequence as set forth in SEQ ID NO:2 is neurolysin and has specific, substantial, credible and well established utility." Applicants obvious disagree in every way and question whether this statement is proper, for it is most certainly inaccurate. The Applicants' present application predates Chen et al. and, in fact, Chen et al. likely have no knowledge of Applicants' efforts or the knockout mouse results described. Given that the present application is still in prosecution, it seems very likely that there are other, both, U.S. and international patent applications in various stages of prosecution addressing the sequences of the present invention, particularly given the well recognized utility of the molecules. Applicants imagine that the Examiner is, as they are, unaware of most, if not all, of these other efforts. The only reasonable conclusion that one might draw from the information that is publically available is that Chen et al. may have been the first to publish "that human protein having the amino acid sequence as set forth in SEQ ID NO:2 is neurolysin and has specific, substantial, credible and well established utility."

Applicants submit that for all of the many reasons provided in the previous section and in previous responses the present invention has been shown to have "a specific, substantial, and credible utility". Applicants therefore respectfully request withdrawal of the rejection of claims 1-5 under 35 U.S.C. § 112, first paragraph.

V. Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

New claim 5 is rejected as improperly dependent from itself. Amendment of Claim 5 has corrected this error. Therefore, Applicants' respectfully request withdrawal of this rejection.

VI. Conclusion

The present document is a full and complete response to the Final Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is now in condition for allowance, and such favorable action is respectfully requested. Should Examiner Walicka have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

This response is timely filed and Applicants believe no fees are due in connection with this response. However, should this be incorrect the Commissioner is authorized to charge any required fees or credit any overpayment to Deposit Account No. 50-0892.

Respectfully submitted,

04/24/03
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Exhibit A

Clean Version of The Pending Claims in U.S. Patent Application Ser. No. 09/833,782

1. (previously amended) An isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1.

2. (previously amended) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO: 2; and

(b) hybridizes under highly stringent conditions including washing in 0.1xSSC/0.1% SDS at 68°C to the nucleotide sequence of SEQ ID NO: 1 or the complement thereof.

3. (original) An isolated nucleic acid molecule comprising a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO:2.

4.(previously added) An expression vector comprising a nucleic acid sequence of Claim 3.

5.(amended) A cell comprising the expression vector of Claim 4.

Exhibit B

Marked Up Version of Amended Claims in U.S. Patent Application Ser. No. 09/833,782

1. (previously amended) An isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1.

2. (previously amended) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO: 2; and

(b) hybridizes under highly stringent conditions including washing in 0.1xSSC/0.1% SDS at 68°C to the nucleotide sequence of SEQ ID NO: 1 or the complement thereof.

3. (original) An isolated nucleic acid molecule comprising a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO:2.

4.(previously added) An expression vector comprising a nucleic acid sequence of Claim 3.

5.(amended) A cell comprising the expression vector of Claim [5]4.